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(21) International Application Number: PCT/HU85/00076 (22) International Filing Date: 20 December 1985 (20.12.85) (71) Applicant (for all designated States except US): INNOVANCE ÁLTALÁNOS INNOVÁCIÓS PÉNZINTÉZET [HU/HU]; Deák Ferenc u. 5, H-1052 Budapest (HU). (72) Inventor; and (75) Inventor/Applicant (for US only) : NOVÁK, Tibor [HU/HU]; Móricz Zs. u. 18, H-6065 Lakitelek (HU). (74) Agent: PATENT AND LAW OFFICE FOR INTERNATIONAL AFFAIRS; P.O. Box 360, H-1369 Budapest (HU). (81) Designated States: AT, AU, BE (European patent), CH, DE, DK, FI, FR (European patent), GB, HU, IT (European patent), JP, NL, NO, SE, US.		Published <i>With international search report.</i>
(54) Title: SKIN CARE COMPOSITIONS HAVING KERATOLYTIC AND ANTIINFLAMMATORY ACTIVITY (57) Abstract Skin care compositions having keratolytic and antiinflammatory activity comprising the extract of the leaf, green stalk and/or flower of <i>Lycium halimifolium</i> as active ingredient.		

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SKIN CARE COMPOSITIONS HAVING KERATOLYTIC AND
ANTIINFLAMMATORY ACTIVITY

The invention relates to skin care compositions having keratolytic and antiinflammatory activity.

5 Background of the invention

Recently more and more so called phytocosmetic skin care compositions are put on the market which contain plant extracts as active ingredient.

10 The aim of the present invention was to find new active ingredients of plant origin for the use in skin care compositions.

The plant *Lycium halimifolium* belongs to the *Lycium* genus. It is native in the basin of the Mediterranean Sea, in Hungary it grows wild. The various
15 *Lycium* species have several names, in many instances it is difficult to discern the individual species.

In the last two decades, mainly from the early seventies *Lycium chinense* and *Lycium europeum* are mentioned in the literature. A great part of the references relate
20 to the various components of the *Lycium* species (C.A. 62, 3064g, 1965; Vopr. Farm., 1, 49-51, 1973; Phytochem., 15, 1701-2, 1976; Syoyakugaku Zasshi, 17, 14-15, 1963, and 20, 481-4, 1969; C.A., 65, 19224f, 1969; Arch. Pharm. 310-1, 35-40, 1977, and 308-8, 653-54, 1975; Pak. J. Sci.
25 Ind. Res., 11-3, 247-49, 1968; Annales Inst. Sup. di Sanita, Roma, 5, 51-53, 1969; Curr. Sci., 50-5, 235, 1981). In other references the physiological properties

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of *Lycium* species are discussed. Osawa and Nunokawa (Niigatu Igakkai Zasshi, 83-2, 82-92, 1969, Nippon Naibumpi Gakkai Zasshi, 46-1, 32-52, 1972) investigated the effect of the extracts prepared from the crop, leaf and root of *Lycium chinense* on the ovulation of rabbits. Sanwa isolated a protein from the aqueous extract of *Lycium chinense* which reduces the cholesterol level of blood (C.A., 94, 71477n, 1981; Kokai 80, 160 723). A compound named cucoamine was isolated from *Lycium chinense* by Japanese researchers which has a significant blood pressure reducing activity (Tetrahedron Letters, 1355-6, 1980). Also the role of *Lycium chinense* in the therapy is mentioned by the authors, accordingly it is used in the east for reducing the blood-sugar level and for antipyresis and its use against stress and ulcus is described as well. According to the investigations of Lapirina (Farmatsevt. Zh., 19-4 52-8, 1964) in animal tests by the use of the extract of *Lycium halimifolium* a long-lasting blood-sugar reducing effect can be achieved. According to the GB patent specifications 1 157 717 and 1 300 966 pharmaceutically active evaporation residue and liquid distillate can be produced by the vacuum distillation of the extracts of plant species, e.g. of *Lycium chinense*. An apparatus is described for carrying out the process but the specifications do not contain any pharmacological data. GB patent specification 1 106 133 relates to a process for the recovery of saponines from plant tissues, e.g. from *Lycium barbarum*. The saponines thus obtained are suitable for treating malignant and non-malignant tumours and *Trichomonas* infections. However there is no reference in the literature to the keratolytic and antiinflammatory

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activity of any of the Lycium species, such as of Lycium halimifolium. Furthermore there is no reference in the literature to any skin care composition having the above activity.

5 Brief description of the invention

During our experiments it has been surprisingly found that by the extraction of the leaf, green stalk and/or flower of Lycium halimifolium an active ingredient solution was obtained which was excellently suitable for the local treatment of keratinized skin, e.g. for the extirpation of verrucae and for calming the inflamed skin when admixed with diluents and/or vehicles and optionally with other known substances used in the cosmetic industry, e.g. propolis.

15 Detailed description of the invention

The present invention relates to skin care compositions having keratolytic and antiinflammatory activity comprising the extract of the leaf, green stalk and/or flower of Lycium halimifolium as active ingredient together with the usual vehicles and/or diluents.

The extract is prepared from the dried and crushed plant with water or with a mixture of water and a water miscible organic solvent, preferably with the mixture of ethanol and water by steeping or boiling. After filtering the extract the solution of the active ingredient is formulated directly or after lyophilization with the usual cosmetic vehicles and/or diluents (e.g. vegetable oils) into cosmetic compositions, e.g. into creams, solutions,

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gels, body powders etc.

The compositions of the invention show new favourable effects.

The gel (Example 12) and the solution (Example 11) were examined on 90 women and 45 men aged from 5 to 45 years having verrucae on the palm or sole (*Verrucae vulgaris*). A group of 35 women and 15 men aged from 4 to 40 years served as control group, this group was treated with a composition comprising of 2.0 g of salicylic acid, 2.0 g of lactic acid, 1.0 g of diethyl ether and 5.0 g of collodium, generally used for the treatment of verrucae. The treatment was carried out twice daily in both groups by applying the compositions to the verrucae, in the evening after the second treatment a bandage was applied. The tensive, inflammatory symptoms of the skin treated with the composition of the invention already on the third day of the treatment were improving, the desquamation of the skin has begun. After a 7-week treatment in 110 cases the verrucae disappeared, in 25 cases improvement was observable. During the treatment no allergic reaction, irritative dermatitis or hypersensitiveness were observed. In the control group after the 7-week treatment the verrucae only in 5 cases disappeared.

The following non-limiting Examples show the compositions of the invention and the preparation of the active ingredient.

Example 1

Leaves and green stalks of *Lycium halimifolium* were dried at 20 °C in a manner usual for herbs, then

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crushed. 1 kg of the crushed substance was boiled for 2 hours in 10 litres of deionized water, the resulting extract was filtered and the filtrate was stored in a dry, cool place until use.

5 Example 2

Leaves and green stalks of *Lycium halimifolium* were dried as in Example 1, then crushed. 1 kg of the crushed substance was boiled for 20 minutes in 8 litres of water, the resulting extract was filtered and the filter cake (drug residue) was pressed with a hydraulic press. 10 The drug was again extracted in the same way with 4 litres of water, the aqueous extracts were combined, filtered and lyophilized. 258 g of dry extract were obtained.

15 Example 3

Leaves and green stalks of *Lycium halimifolium* were dried as in Example 1, then crushed. 1 kg of the crushed substance was steeped for 36 hours in 5.0 litres of 70 % by vol. aqueous ethanol. Then the extract 20 was filtered and stored in a dry, cool place until use.

Example 4

Leaves, green stalks and flowers of *Lycium halimifolium* were dried as in Example 1, then crushed. 1 kg of the crushed substance was boiled for 20 minutes in 25 5 litres of water, the extract was filtered and stored in a dry, cool place until use.

Example 5

Flowers of *Lycium halimifolium* were dried as in Example 1, then crushed. 1 kg of the crushed substance

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was steeped for 12 hours at room temperature in 5 litres of deionized water. The extract was filtered and stored in a dry, cool place until use.

Example 6

5 Skin care cream

Components

	Extract of Example 1	20.00 g
	sodium laurylsulfate	1.00 g
	Nipagine	0.10 g
10	adeps lanae	7.00 g
	vaselinum album	7.00 g
	oleum helianti	3.00 g
	oleum ricini	3.00 g
	glycerol	5.00 g
15	deionized water	53.80 g
	geranium oil	0.10 g

The components, excluding the active ingredient and geranium oil, are mixed, the mixture is molten on a water bath, heated to the boiling point, then cooled
20 under constant stirring, the water evaporated in the course of heating is supplemented. The active ingredient and geranium oil are added to the mixture in small portions and the mixture is homogenized.

Example 7

25 Skin care cream

Components

	Extract of Example 2	2.65 g
	sodium laurylsulfate	1.00 g
	Nipagine	0.10 g
30	adeps lanae	7.00 g

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	vaselinum album	7.00 g
	oleum helianti	3.00 g
	oleum ricini	3.00 g
	glycerol	5.00 g
5	propolis	0.11 g
	geranium oil	0.24 g
	deionized water	71.00 g

The cream is prepared according to Example 6.

Example 8

10 Skin care cream

Components

	Extract of Example 5	5.00 g
	sodium laurylsulfate	1.00 g
	Nipagine	0.10 g
15	adepts lanae	7.00 g
	vaselinum album	7.00 g
	oleum helianti	3.00 g
	oleum ricini	3.00 g
	glycerol	5.00 g
20	geranium oil	0.10 g
	deionized water	68,80 g

The cream is prepared according to Example 6.

Example 9

Body lotion

25	Components	
	Extract of Example 1	95.00 g
	Nipagine	0.10 g
	glycerol	4.50 g
	geranium oil	0.40 g

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Nipagine, then glycerol and geranium oil are added to the extract of Example 1, the mixture is homogenized, sterilized by filtration and filled into ampoules or flasks under sterile conditions or it is formulated by means of a propellant into sprays form.

Example 10

Body lotion

Components	
Extract of Example 3	50.00 g
10 Nipagine	0.20 g
sodium laurylsulfate	0.05 g
glycerol	4.45 g
deionized water	45.20 g
geranium oil	0.10 g

15 The solid components are dissolved in the deionized water, glycerol and geranium oil are added to the solution, the solution is homogenized, sterilized by filtration and it is formulated according to Example 9.

Example 11

20 Body lotion

Components	
Extract of Example 4	5.00 g
Nipagine	0.10 g
glycerol	5.00 g
25 geranium oil	0.10 g
deionized water	89.80 g

Deionized water is homogenized with glycerol and Nipagine, the extract of Example 4 is added thereto, finally geranium oil is added, the solution is homogenized, sterilized by filtration and formulated according to Example 9.

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Example 12

Gel

Components

	Extract of Example 1	50.00 g
5	Carbopol 940 (gel forming polymer)	2.00 g
	propylene glycol	10.00 g
	sodium hydroxide	0.10 g
	Nipagine	0.10 g
	geranium oil	0.10 g
10	deionized water	37.70 g

The extract of Example 1 is mixed with the deionized water, propylene glycol and Nipagine, then Carbopol 940 is added to the above mixture. It is allowed to swell for 10 hours, then it is homogenized, sodium hydroxide is added under stirring to the homogenizate in the form of a 10 % aqueous solution, finally geranium oil is added and the mixture is homogenized.

Example 13

20 A gel is prepared according to Example 12 with the exception that as active ingredient 50.00 g of the extract of Example 4 is used.

Example 14

Body powder

25 4.5 g of the extract of Example 2 are homogenized with 95.25 g of talc and 0.25 g of menthol. The mixture is sterilized by UV radiation, then it is formulated under sterile conditions.

Claims

1. Skin care compositions having keratolytic and antiinflammatory activity comprising the extract of the leaf, green stalk and/or flower of *Lycium halimifolium* as active ingredient together with the usual cosmetic vehicles and/or diluents.
2. Compositions according to claim 1 comprising the extract of the leaf and green stalk of *Lycium halimifolium* as active ingredient.
3. Compositions according to claim 1 comprising the extract of the flower of *Lycium halimifolium* as active ingredient.
4. Compositions according to claim 1 comprising the extract of the leaf, green stalk and flower of *Lycium halimifolium* as active ingredient.
5. Process for the preparation of skin care compositions having keratolytic and antiinflammatory activity characterized in that the leaf, green stalk and/or flower of *Lycium halimifolium* after having been dried is/are crushed then extracted with water or with a mixture of water and a water miscible organic solvent, preferably with the mixture of water and ethanol and after filtration the solution of the active ingredient thus obtained is admixed directly or after lyophilization with the usual vehicles and/or diluents.
6. The process according to claim 5, characterized in that the extraction is carried out at a temperature of from 20 °C to 100 °C.
7. The process according to claims 5 or 6 characterized in that the extraction is carried out at about 100 °C for 20 to 120 minutes.

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8. The process according to claims 5 or 6 characterized in that the extraction is carried out at about 20 °C for 12 to 36 hours.

INTERNATIONAL SEARCH REPORT

International Application No PCT/HU 85/00076

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC <div style="text-align: center; font-family: monospace;">IPC⁴: A 61 K 7/48, 35/78</div>														
II. FIELDS SEARCHED <div style="text-align: center; font-size: small;">Minimum Documentation Searched ⁷</div> <table style="width: 100%; border: none;"> <tr> <td style="width: 30%; border-bottom: 1px solid black; font-size: x-small;">Classification System</td> <td style="border-bottom: 1px solid black; font-size: x-small;">Classification Symbols</td> </tr> <tr> <td style="border-right: 1px solid black; padding: 5px;">Int.Cl.⁴</td> <td style="padding: 5px;">A 61 K 7/48, 35/78</td> </tr> </table> <div style="text-align: center; font-size: x-small; margin-top: 10px;">Documentation Searched other than Minimum Documentation to the extent that such Documents are included in the Fields Searched ⁸</div>			Classification System	Classification Symbols	Int.Cl. ⁴	A 61 K 7/48, 35/78								
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III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table style="width: 100%; border: none;"> <tr> <td style="width: 10%; border-bottom: 1px solid black; font-size: x-small;">Category ¹⁰</td> <td style="width: 70%; border-bottom: 1px solid black; font-size: x-small;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</td> <td style="width: 20%; border-bottom: 1px solid black; font-size: x-small;">Relevant to Claim No. ¹³</td> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">A</td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">GB, A, 1 106 133 (J.J. JOSEPH BALANSARD et al.) 13 March 1968 (13.03.68), see page 3, line 98 - page 4, line 19.</td> <td style="vertical-align: top; padding: 5px;">(5)</td> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">A</td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;">Ullmanns Encyklopädie der technischen Chemie, vol. 6, published 1955, by Urban & Schwarzenberg (München-Berlin), see pages 23-42, especially pages 37-42.</td> <td style="vertical-align: top; padding: 5px;">(5)</td> </tr> <tr> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px;"></td> <td style="border-right: 1px solid black; vertical-align: top; padding: 5px; text-align: center;">----</td> <td style="vertical-align: top; padding: 5px;"></td> </tr> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	GB, A, 1 106 133 (J.J. JOSEPH BALANSARD et al.) 13 March 1968 (13.03.68), see page 3, line 98 - page 4, line 19.	(5)	A	Ullmanns Encyklopädie der technischen Chemie, vol. 6, published 1955, by Urban & Schwarzenberg (München-Berlin), see pages 23-42, especially pages 37-42.	(5)		----	
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<div style="font-size: x-small;"> ¹⁰ Special categories of cited documents: ¹⁰ "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "A" document member of the same patent family </div>														
IV. CERTIFICATION <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border-bottom: 1px solid black; font-size: x-small;">Date of the Actual Completion of the International Search</td> <td style="width: 50%; border-bottom: 1px solid black; font-size: x-small;">Date of Mailing of this International Search Report</td> </tr> <tr> <td style="text-align: center; padding: 5px;">24 July 1986 (24.07.86)</td> <td style="text-align: center; padding: 5px;">29 July 1986 (29.07.86)</td> </tr> <tr> <td style="border-bottom: 1px solid black; font-size: x-small;">International Searching Authority</td> <td style="border-bottom: 1px solid black; font-size: x-small;">Signature of Authorized Officer</td> </tr> <tr> <td style="text-align: center; padding: 5px;">AUSTRIAN PATENT OFFICE</td> <td style="text-align: center; padding: 5px;"> </td> </tr> </table>			Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	24 July 1986 (24.07.86)	29 July 1986 (29.07.86)	International Searching Authority	Signature of Authorized Officer	AUSTRIAN PATENT OFFICE					
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Anhang zum internationalen Recherchenbericht über die internationale Patentanmeldung Nr.

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Annex to the International Search Report on International Patent Application No. PCT/HU 86/00076

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Annexe au rapport de recherche internationale relatif à la demande de brevet international n°.

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Im Recherchenbericht angeführtes Patent- dokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
GB-A-1 106 133	13/03/1968	None	